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METABOLIC PECULIARITIES IN NORMAL YOUNG MEN AS REVEALED BY REPEATED BLOOD ANALYSES

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Physiologists and biochemists have for decades been engaged in trying to construct a *single picture* which will represent the way in which the body of a normal human being functions. As a result of this approach, a tremendous volume of information and insight has been amassed, which, of course, it would be impossible to summarize in a short space. The task of constructing this picture, even leaving out all complications, is an extremely difficult one and very far from completed. It needs to be carried forward continuously.

This approach, however, leaves out of consideration certain serious complications to which we wish to draw attention. Largely because of our ardent attempts to develop a statistically valid *single picture*, a tremendous number of physiological difficulties which human beings encounter are almost as little understood today as they were decades ago, before we became acquainted with microbial infections, virus infections, and specific nutritional deficiencies. We have learned to classify the many different kinds of invading organisms and viruses and to recognize among them not only species differences but important and crucial strain differences. We have made very little progress, however, in learning how to classify people with respect to their susceptibility to metabolic or infective diseases; yet we recognize

in an academic way that variation within the human family is very great and that, regardless of whether the disease is metabolic or infective, marked differences in susceptibility exist.

Our reference to the little-understood physiological difficulties which people often encounter has to do with medical problems: multiple sclerosis, muscular dystrophy allergies, arthritis, arteriosclerosis, heart failure, cancer, and various forms of mental disease, including schizophrenia. While for many of these diseases we may know the immediate precipitating causes and may be able to institute palliative measures we are still very much in the dark as to the fundamental bases on which the existence of these diseases rests.

This darkness may gradually be dispelled as the result of innumerable research contributions which are not consciously or specifically related to the central theme of our discussion, but the desired end will come much more rapidly if we physiologists and biochemists can be diverted sufficiently from our search for the attributes of a normally functioning individual so that some substantial attention can be devoted to studying the distinctive attributes possessed by real individuals.

We submit as a working hypothesis the idea that there is only one place to search for the key attributes which make certain individuals susceptible to arthritis, allergies, heart disease, cancer, mental disease, etc.; this is *in individuals*. By concentrating on the statistical "single picture" referred to above, we bar ourselves from finding the distinctive attributes which make for susceptibility to numerous specific diseases, including many that laymen rarely hear of.

In this connection it is well to remind ourselves that susceptibility to disease concerns the majority; it is not a minority problem. Most individuals exhibit susceptibility to one or more diseases, and this susceptibility is often of a specific nature. Obstetricians are happy when they can inform the mother that her baby is "normal." But when normal infants mature, they usually develop into adults who, because of specific susceptibilities, become diseased.

What is needed, in the authors' opinion, is a new approach which will utilize the vast knowledge that has accumulated but which will disregard, for the time being, the time-honored philosophy which centers its attention on the normal (reference) man. When we study chemistry, we learn about the behavior of all kinds of chemicals, their similarities and their differences. When we study microbiology, likewise, we learn about microörganisms, their likenesses and their differences. We carry out our studies of these subjects for the most part inductively—that is, we make observations first, and then we formulate our generalizations on the basis of these observations. When in human physiology we adopt the philosophy of the "single picture," the reference man, we reverse this procedure; we first *assume* that the reference individual is the center of interest; then we make observations and apply statistics in an attempt to find out what the reference individual is like.

The importance of this single-picture philosophy is indicated by the fact that it is implicitly accepted by the authors of practically every treatise and monograph dealing with physiology, biochemistry, pharmacology, and physiological psychology and by the authors of most journal articles in these fields.

The purpose of the present investigation is to make a beginning in a long-range inductive approach which we are confident will contribute greatly to the understanding of diseases of which the etiologies are now obscure. We have studied

inductively and individually a group of young men who are at present well and normal, with the full realization that they may have in them the roots of disease susceptibility, particularly susceptibility to metabolic disease. We have explored within this group of well young men for the existence of distinctive blood characteristics which may be associated with disease susceptibility or disease resistance.

At this stage in the development of this new approach, we regard the mere existence of metabolic peculiarities in so-called "normal" young men as sufficiently important to merit attention. To postulate or guess what diseases specific peculiarities may foreshadow would be abandoning induction for premature deduction. If we can offer convincing evidence that distinctive and suggestive attributes exist in young men who are at present healthy, other investigators will be induced to follow this lead by searching in a hundred ways for these individual characteristics which are probably closely related to disease susceptibility. Research directed to this end has in the past been practically nonexistent. While much research in the broad area which includes physiology, biochemistry, and physiological psychology has necessarily been concerned with individuals, the information obtained has been regarded as valuable and scientific only when it applies to the reference man.

A total of twelve healthy young men were involved in this study.[1] Of these, eight were studied more thoroughly than the other four. From each of the eight individuals, five or six fasting samples of blood were drawn at weekly or longer intervals, and each sample was analyzed by conventional, recognized clinical methods for glucose, lactic acid, creatinine, urea, uric acid, amylase, lipase, acid phosphatase, alkaline phosphatase, acetyl cholinesterase, inorganic phosphate, sodium, potassium, calcium, and magnesium. The corpuscles from each blood sample were also analyzed for sodium, potassium, calcium, and magnesium. The character of the results can best be judged by a consideration of Figures 1–9.

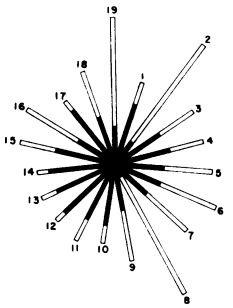
In Figure 1 is given the accumulated information taken from the best obtainable values from the literature on the items included in our study as they pertain to the reference (normal) man. Graphed in terms of polar co-ordinates, the length of each line represents on an appropriate scale the amount of each constituent found in the blood of normal man. The unshaded portion of each line represents the range observed when samples of blood from normal men are analyzed.

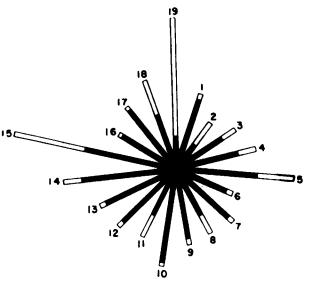
In Figures 2–9 are graphed the corresponding data with respect to the eight young men most thoroughly studied. A careful inspection of these graphs shows that each one of the eight individuals exhibits at least one peculiarity of the sort which may be important in connection with his distinctive susceptibility or resistance to a specific metabolic (or infective) disease. The specific peculiarities which stand out in this study are listed in Table 1.

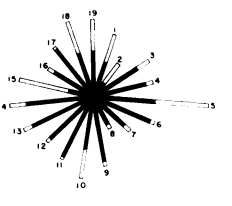
TABLE 1

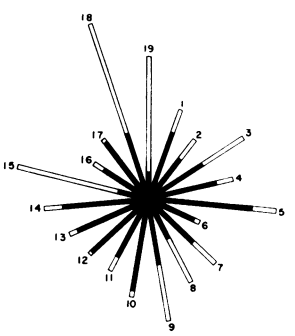
OBSERVED PECULIARITIES IN BLOOD COMPOSITION

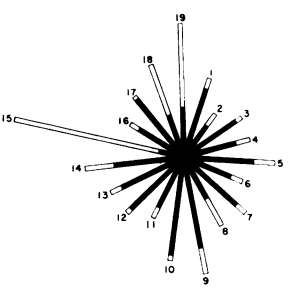
High	Low	Highly Variable	Conspicuously Constant
Plasma Mg (WDB)	Plasma Mg (KH)	Plasma Mg (RWS)	Cell Na (WDB)
Plasma K (RN)		Plasma Ca (WS)	Cell Ca (RG)
Uric acid (SK)		Cell Ca (SK)	
Alkaline phosphatase (RWS)		Creatinine (SK)	
		Lipase (GD)	
		Acetylcholinesterase (RN)	

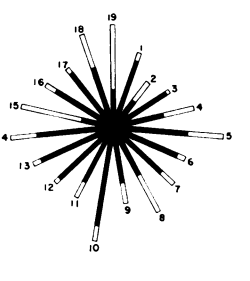


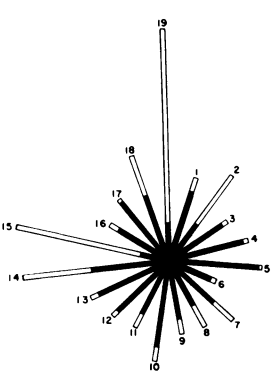


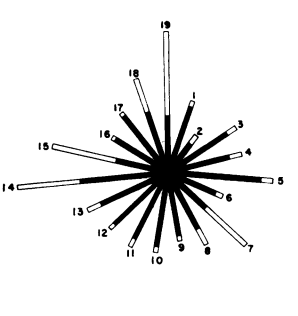


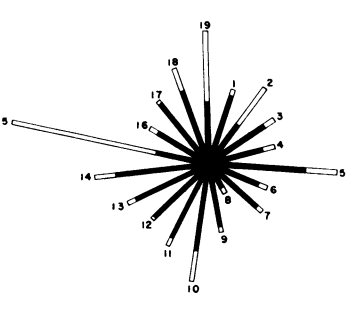












FIGS. 1–9.—Blood components: *1*, glucose; *2*, lactic acid; *3*, creatinine; *4*, urea; *5*, uric acid; *6*, amylase; *7*, lipase; *8*, acid phosphatase; *9*, alkaline phosphatase; *10*, acetylcholinesterase; *11*, inorganic phosphate; *12*, sodium (plasma); *13*, potassium (plasma); *14*, calcium (plasma); *15*, magnesium (plasma); *16*, sodium (cell); *17*, potassium (cell); *18*, calcium (cell); *19*, magnesium (cell).

The inclusion of "highly variable" items and "conspicuously constant" items among the observed peculiarities is justified, first, by the fact that they unquestionably stand out as distinctive for the individuals concerned and, second, by the fact that there are already strong hints, from work both in our laboratory[2] and elsewhere,[3] that this type of peculiarity may be significant in connection wth disease susceptibility.

Elementary statistical considerations make our findings reasonable. The idea that a normal young man will exhibit about average values when tested in a number

of different independent ways is bound to be in error. An individual young man selected at random will have one chance in two of being within the median 50 per cent with respect to his fasting blood glucose level. He will have one chance in four of being within the median 50 per cent with respect to his glucose level *and* his lactic acid level. He will have one chance in eight of being within the median 50 per cent with respect to three independent items. When one considers as many as nineteen items, the number we have included in our study, the chance of any individual's being within the middle 50 per cent range with respect to all nineteen items (assuming that they are independent measures) would be less than one in a half-million.

These considerations bring into bold relief the important difference between "statistical man" and any individual man. Statistical man, by definition, is about average in every respect; real men are likely to deviate markedly from the average in many respects. If it were possible to produce a synthetic statistical man, there is no telling what he would be like. Undoubtedly he would be extraordinary; possibly he would lack susceptibility to disease. Real individuals, on the other hand, have peculiarities in metabolism as well as disease susceptibilities, and it seems reasonable to suppose, as a working hypothesis, that the peculiarities and the susceptibilities are closely related. It also seems reasonable to hope, on the basis of the genetotrophic concept,[4] that many diseases of obscure etiology can be successfully attacked once we are acquainted with their biochemical nature.

The fact that enzyme levels in the blood are characteristically different for different individuals clearly indicates that the body chemistry of each individual is distinctive. While the total metabolism of each of two men of about average height and weight, measured in calories, may be about the same and very close to that of statistical man, the details of the metabolism of each may be highly distinctive. Some specific chemical reactions may be taking place in one individual ten times as fast as they are in another.[5] If this is true, surely this must be the basis for differences in disease susceptibility.

It is perhaps belaboring the obvious to say that there are a multitude of ways in which these or any other young men could be studied, quite aside from our particular study. Each method of study would reveal additional evidence of the importance of individuality—a concept which commonly receives lip service but very little scientific attention.[6]

If the concept of statistical man is of limited significance in connection with susceptibility to metabolic diseases, it is also of limited value in many other areas in which human problems arise. It is no wonder that, in the social sciences generally, the concept of humanity is based upon the scientifically determined characteristics of statistical man as postulated by the biological sciences. There must be a revolution in our thinking not only in medicine but in the social field as well; statistical man must be dethroned from his position as the center of our interest. On the basis of our study and observations he finds no counterpart in a population of real individuals. If we think that a typical human population consists of individuals who are "about average" in most respects, our thinking is bound to be unrealistic and futile, because a typical human population contains no such individuals.

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[4] R. J. Williams, E. Beerstecher, Jr., and L. J. Berry, *Lancet*, p. 287, February 18, 1950.

[5] R. J. Williams, *Origins of Resistance to Toxic Agents* (New York: Academic Press, Inc., 1955), p. 200.

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*NYBOMYCIN, A NEW ANTIBIOTIC WITH ANTIPHAGE AND ANTIBACTERIAL PROPERTIES**

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Culture liquids of a streptomycete, A 717, isolated from Missouri soil, were reported earlier to have a broad antiphage spectrum. Concentrates prepared from the culture liquid were found to have no effect on PR8 influenza or on SK polio virus.[1]

In further investigations a colorless crystalline compound with antiphage and antibacterial activity was isolated from the culture liquid and mycelium of A 717. It has been named *nybomycin*. The production, isolation, and some of the properties of nybomycin are described in this report.

Culture and Production.—The streptomycete A 717 was maintained on oatmeal agar. On agar plates the culture was tan to brownish, with slight droplet production; the undersurface was pink to reddish brown. For production of nybomycin the organism was grown in submerged aerated culture at room temperature in a potato extract medium.[2] Antiphage activity generally appeared on the third or fourth day, at which time the pH of the culture fluid was 7.2–8.2. The active substance was present in the mycelium and in the culture liquid in about equal amounts, the proportion varying with the age of the culture at the time of harvest.

Purification and Chemical Properties.—Isolation and purification of nybomycin was followed by assay with *Bacillus cereus* phage as the test organism, using the paper disk method.[1] The mycelium was collected on a Buchner funnel, washed with water, and then extracted several times with boiling 95 per cent ethanol. The combined extracts were taken to dryness *in vacuo* and treated successively with boiling Skellysolve C (a petroleum ether fraction of boiling range 80–100° C.), cold ether, and cold acetone, all of which removed colored impurities. The residue was extracted with boiling 95 per cent ethanol, which, on cooling, deposited grayish-white crystals of crude nybomycin.

The culture liquid, free of mycelium, was adjusted to pH 6.0 and extracted several times with *n*-butanol, or it was acidified to pH 2.5, filtered, and extracted with one-half its volume of chloroform. Considerable loss was experienced with the latter method because, on acidification, a precipitate containing active material was formed from which the compound could not be isolated. The extracts in bu-